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(54) Title: NOVEL ARYL UREIDO BENZOIC ACID DERIVATIVES AND THEIR USE

(57) Abstract: This invention relates to novel aryl ureido benzoic acid derivatives useful as selective and non-competitive antagonists of the ionotropic GluR5 receptor. Due to their biological activity, the aryl ureido derivatives of the invention are considered useful for treating diseases that are responsive to modulation of an aspartate or a glutamate receptor. Moreover the invention provides chemical compounds for use according to the invention, as well as pharmaceutical compositions comprising the chemical compounds, and methods of treating diseases or disorders or conditions responsive to modulation of an aspartate or a glutamate receptor.

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# NOVEL ARYL UREIDO BENZOIC ACID DERIVATIVES AND THEIR USE

## TECHNICAL FIELD

5 This invention relates to novel aryl ureido benzoic acid derivatives useful as selective and non-competitive antagonists of the ionotropic GluR5 receptor.

Due to their biological activity, the aryl ureido derivatives of the invention are considered useful for treating diseases that are responsive to modulation of an aspartate or a glutamate receptor.

10 Moreover the invention provides chemical compounds for use according to the invention, as well as pharmaceutical compositions comprising the chemical compounds, and methods of treating diseases or disorders or conditions responsive to modulation of an aspartate or a glutamate receptor.

## 15 BACKGROUND ART

Excitatory neurotransmission in the mammalian central nervous system (CNS) is primarily mediated by the amino acid, L-glutamate, acting on ionotropic and metabotropic receptors. The ionotropic receptors, which respond to this amino acid, 20 have been divided into the N-methyl-D-aspartate (NMDA) receptors, the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and the kainic acid (KA) receptors. Moreover molecular biological studies have established that these receptors are composed of subunits that can assemble to form functional channels, and a number of such subunits have been identified.

25 This way it has been established that the AMPA receptors are assembled from four protein subunits known as GluR1 to GluR4, while the KA receptors are assembled from subunits known as GluR5 to GluR7, KA-1 and KA-2.

Due to their distribution in different mammalian tissues, the GluR5 receptors and the substances acting thereon have drawn particular attention.

30 WO 94/22807 describes urea and amide derivatives useful as potassium channel openers.

WO 97/45400, WO 97/45111, WO 98/47879 and WO 00/24707 describe diphenyl urea derivatives containing an acidic group and their use as chloride channel blockers.

35 WO 02/039987 describes the use of diphenyl urea derivatives as malaria anion channel blockers for treating malaria.

WO 02/064128 describes the use of diphenyl urea derivatives for modulation of the association of caspase-9 to Apaf-1 for the treatment of diseases characterised by excessive or insufficient cell death.

WO 02/070467 describes diphenyl urea derivatives useful as inhibitors of intracellular protein-degradation pathways.

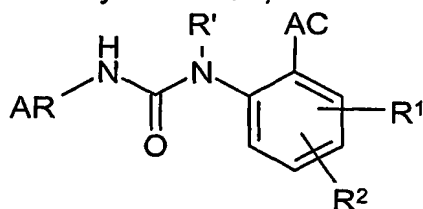
However, use of diphenyl urea derivatives as ionotropic GluR5 receptor modulators have never been described.

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## SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds useful as selective and non-competitive antagonists of the ionotropic GluR5 receptor.

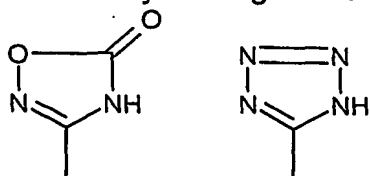
10 This object is met by the provision of the novel aryl ureido benzoic acid derivatives derivative represented by Formula I,



any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

15 AC represents an acidic group selected from  $-\text{SO}_2\text{OH}$ ;  $-\text{SO}_2\text{NH}_2$ ; a group of the formula  $-(\text{CH}_2)_n\text{COOH}$ , wherein  $n$  is 0, 1, 2 or 3; a group of the formula  $-(\text{CX})\text{OH}$ , wherein  $X$  represents O or  $\text{NR}''$ , wherein  $\text{R}''$  represents hydrogen or alkyl; or  $X$  together with  $\text{R}'$  form a heterocyclic ring; and

a heterocyclic ring of the structure



20 , or ; and

$\text{R}'$  represents hydrogen or alkyl; or  $\text{R}'$  and  $X$  together form a heterocyclic ring; and

$\text{R}^1$  and  $\text{R}^2$ , independently of each other, represents hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, haloalkyl, nitro or cyano; and if one of  $\text{R}^1$  and  $\text{R}^2$  represents 25 hydrogen, then the other of  $\text{R}^1$  and  $\text{R}^2$  is different from hydrogen; and

$\text{AR}$  represents an aromatic mono-, bi- or polycyclic carbocyclic or heterocyclic group, which aromatic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or 30 benzyl; or which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-\text{O}-(\text{CH}_2)_m-\text{O}-$ , wherein  $m$  is 1, 2 or 3.

In another aspect the invention provides pharmaceutical compositions comprising therapeutically effective amounts of a chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof.

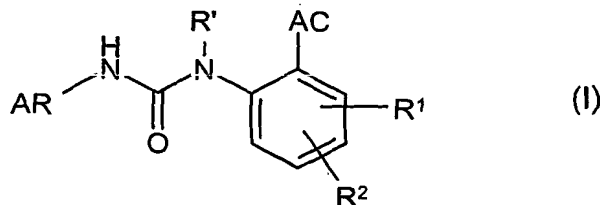
In a further aspect the invention relates to the use of a chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament.

In a final aspect, the invention provides a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of an aspartate or a glutamate receptor, which method comprises the step of administering to said animal body in need thereof a therapeutically effective amount of a chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

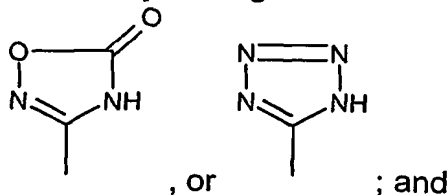
## DETAILED DISCLOSURE OF THE INVENTION

In its first aspect the invention provides an aryl ureido derivative represented by Formula I,



any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

AC represents an acidic group selected from  $-\text{SO}_2\text{OH}$ ;  $-\text{SO}_2\text{NH}_2$ ; a group of the formula  $-(\text{CH}_2)_n\text{COOH}$ , wherein  $n$  is 0, 1, 2 or 3; a group of the formula  $-(\text{CX})\text{OH}$ , wherein  $X$  represents O or  $\text{NR}''$ , wherein  $\text{R}''$  represents hydrogen or alkyl; or  $X$  together with  $\text{R}'$  form a heterocyclic ring; and a heterocyclic ring of the structure

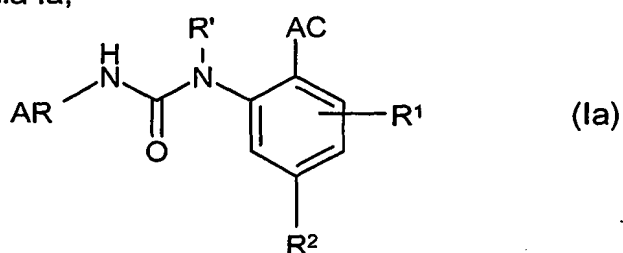


$\text{R}'$  represents hydrogen or alkyl; or  $\text{R}'$  and  $X$  together form a heterocyclic ring; and

$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

AR represents an aromatic mono-, bi- or polycyclic carbocyclic or heterocyclic group, which aromatic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3.

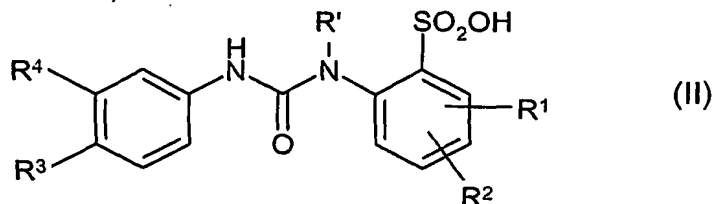
In a preferred embodiment the aryl ureido derivative of the invention is represented by Formula Ia,



wherein  $R'$ ,  $R^1$ ,  $R^2$ , AC and AR are as defined above.

In another preferred embodiment the aryl ureido derivative of the invention is represented by Formula I or Ia, wherein AR represents an aromatic mono-, bi- or polycyclic carbocyclic group, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3.

In a more preferred embodiment, the aryl ureido derivative of the invention is represented by Formula II,



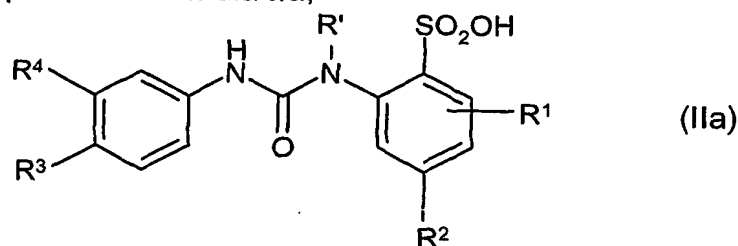
wherein  $R'$  represents hydrogen or alkyl;

$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or  $R^3$  and  $R^4$

together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

In a more preferred embodiment the aryl ureido derivative of the invention is a compound of Formula II, wherein  $R'$  represents hydrogen; and  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl or cycloalkyl; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano or phenyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

In an even more preferred embodiment the aryl ureido derivative of the invention is a compound of Formula IIa,



wherein,

$R'$  represents hydrogen or alkyl;

$R^1$  represents hydrogen, halo, alkyl or cycloalkyl;

$R^2$  represents halo, alkyl or cycloalkyl; and

$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

In a most preferred embodiment, the aryl ureido derivative of the invention is 2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-5-methyl-benzenesulfonic acid;

4-Chloro-5-methyl-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic

acid;

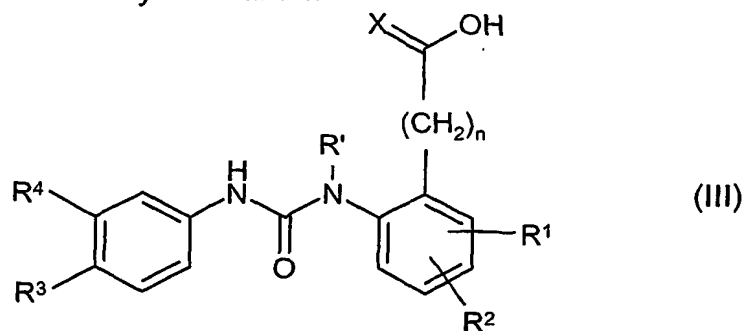
4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic acid;

2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-benzenesulfonic acid; or

4-Chloro-5-methyl-2-(3-naphthalen-2-yl-ureido)-benzenesulphonic acid;

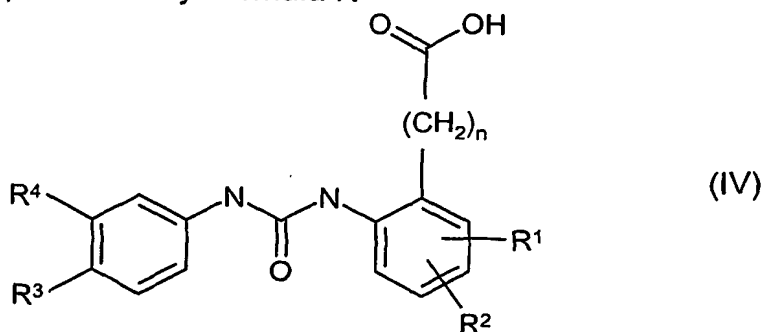
or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

In a third preferred embodiment, the aryl ureido derivative of the invention is a compound represented by Formula III



5 wherein  $n$  is 0, 1 or 2;  $X$  represents O or  $NR''$ , wherein  $R''$  represents hydrogen or alkyl; or  $R'$  and  $X$  together form a heterocyclic ring, which heterocyclic ring may in particular be a pyrazole, an isoxazole or a pyridazole ring; and  $R'$  represents hydrogen or alkyl; or  $R'$  and  $X$  together form a heterocyclic ring, which heterocyclic ring  
 10 may in particular be a pyrazole, an isoxazole or a pyridazole ring; and  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy,  
 15 alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or  
 20 benzyl.

In a fourth preferred embodiment, the aryl ureido derivative of the invention is a compound represented by Formula IV

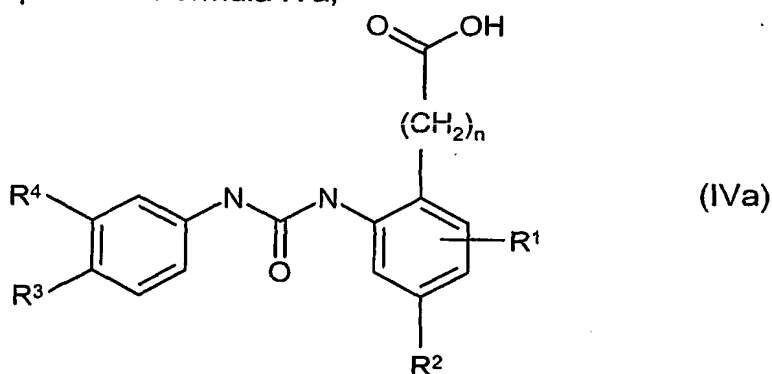


25 wherein  $n$  is 0, 1 or 2; and  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen;

and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

In a more preferred embodiment, the aryl ureido derivative of the invention is a compound of Formula IV, wherein  $n$  is 0, 1 or 2; and  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl or cycloalkyl; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl, nitro, cyano or phenyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

In an even more preferred embodiment, the aryl ureido derivative of the invention is a compound of Formula IVa,



20

wherein

$n$  is 0 or 1;

$R^1$  represents hydrogen, halo, alkyl or cycloalkyl;

$R^2$  represents halo, alkyl or cycloalkyl; and

$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl or phenyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

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In a most preferred embodiment, the aryl ureido derivative of the invention is

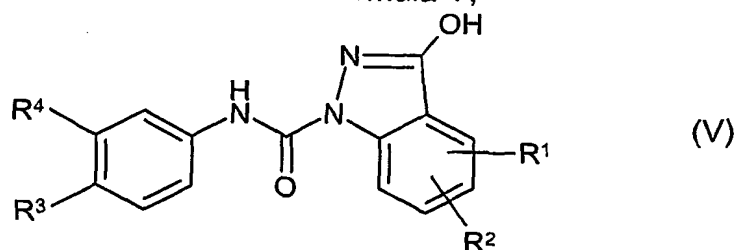
4-Chloro-2-(3-phenyl-ureido)-benzoic acid;

4-Chloro-2-[3-(2-methoxy-phenyl)-ureido]-benzoic acid;



- 2-(3-Benzo[1,3]dioxol-5-yl-ureido)-4-chloro-benzoic acid;  
 4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzoic acid;  
 2-(3-Biphenyl-2-yl-ureido)-4-chloro-benzoic acid;  
 2-(3-Biphenyl-4-yl-ureido)-4-chloro-benzoic acid;  
 5 2-[3-(2-Bromo-phenyl)-ureido]-4-chloro-benzoic acid;  
 4-Chloro-2-[3-(4-fluoro-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(4-iodo-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid;  
 10 4-Chloro-2-[3-(4-methoxy-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(2-trifluoromethyl-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-(3-naphtalen-2-yl-ureido)-benzoic acid;  
 4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid;  
 15 2-(3-Biphenyl-3-yl-ureido)-4-chloro-benzoic acid;  
 4-Chloro-2-[3-(4-hydroxy-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(3-hydroxy-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(2-hydroxy-phenyl)-ureido]-benzoic acid; or  
 {2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-phenyl}-acetic acid;  
 20 or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

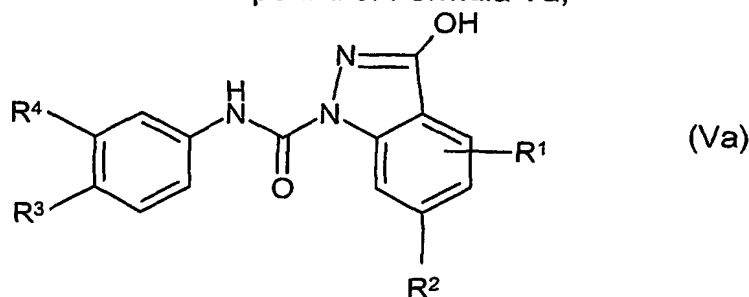
In a fifth preferred embodiment, the aryl ureido derivative of the invention is a phenyl carbamoyl indazole derivative of Formula V,



- 25 wherein  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or  
 30  $R^3$  and  $R^4$  together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

In a more preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula V, wherein  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl or cycloalkyl; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl, nitro, cyano or phenyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

In an even more preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula Va,



wherein

$R^1$  represents hydrogen, halo, alkyl or cycloalkyl;

$R^2$  represents halo, alkyl or cycloalkyl; and

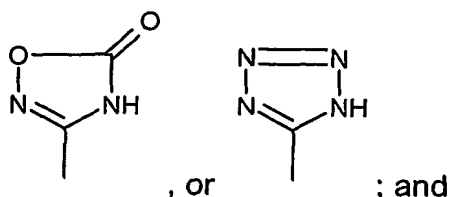
$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl, nitro, cyano or phenyl; or  $R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

In a most preferred embodiment the aryl ureido benzoic acid derivative of the invention is

6-Chloro-3-hydroxy-indazole-1-carboxylic acid naphthalen-2-ylamide;

or an enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable addition salt thereof.

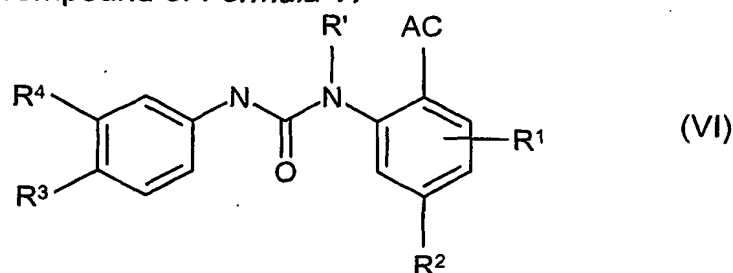
In a sixth preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula I or Ia, wherein AC represents a heterocyclic ring of the structure



R' represents hydrogen or alkyl; and R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen; and

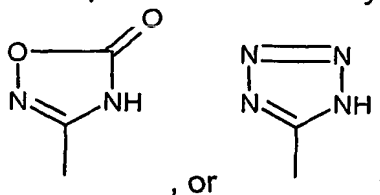
- 5 AR represents an aromatic mono-, bi- or polycyclic carbocyclic or heterocyclic group, which aromatic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or which aromatic group is optionally substituted with a methylenedioxy group  
10 or a higher homolog of the structure -O-(CH<sub>2</sub>)<sub>m</sub>-O-, wherein m is 1, 2 or 3.

In a seventh preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula VI



wherein

- 15 AC represents a heterocyclic ring of the structure



R' represents hydrogen or alkyl;

R<sup>1</sup> represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano;

R<sup>2</sup> represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

- 20 R<sup>3</sup> and R<sup>4</sup>, independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl or phenyl; or R<sup>3</sup> and R<sup>4</sup> together form a methylenedioxy ring of the structure -O-CH<sub>2</sub>-O-; or R<sup>3</sup> and R<sup>4</sup> together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

- 25 In a most preferred embodiment the aryl ureido benzoic acid derivative of the invention is

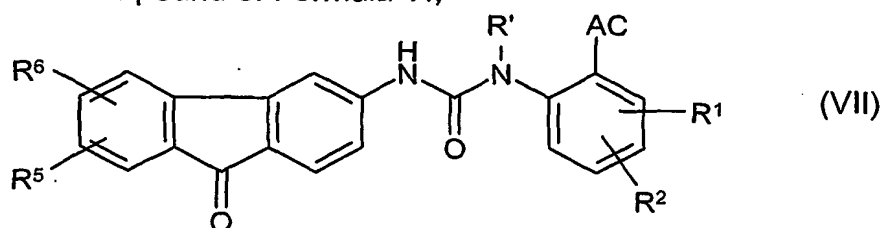
1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea;

- 30 1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-bromo-phenyl)-urea;

1-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-3-naphthalen-2-yl-urea; or  
1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-naphthalen-2-yl-urea;

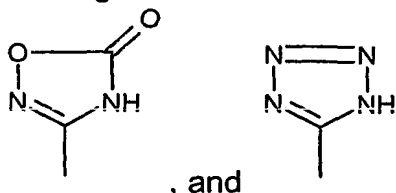
or an enantiomer or a mixture of enantiomers, or a pharmaceutically-  
5 acceptable addition salt thereof.

In an eight preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula VI,



wherein AC represents an acidic group selected from

10 -SO<sub>2</sub>OH; -SO<sub>2</sub>NH<sub>2</sub>; a group of the formula -(CH<sub>2</sub>)<sub>n</sub>COOH, wherein n is 0, 1, 2 or 3; a group of the formula -(CX)OH, wherein X represents O or NR', wherein R' represents hydrogen or alkyl; or X together with R' form a heterocyclic ring, which heterocyclic ring may in particular be a pyrazole, an isoxazole or a pyridazole ring; and a heterocyclic ring of the structure



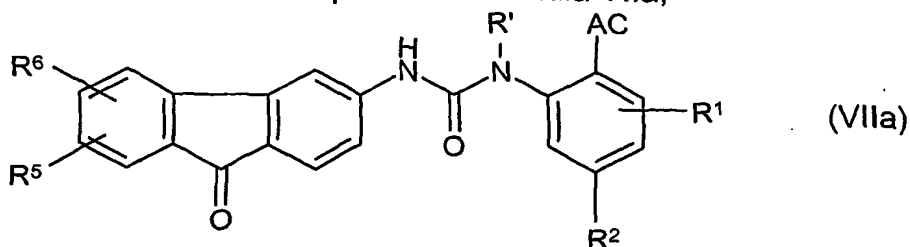
15 R' represents hydrogen or alkyl; or R' and X together form a heterocyclic ring, which heterocyclic ring may in particular be a pyrazole, an isoxazole or a pyridazole ring;

R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen;

R<sup>5</sup> and R<sup>6</sup>, independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or R<sup>5</sup> and R<sup>6</sup> together form a methylenedioxy ring or a higher  
25 homolog of the structure -O-(CH<sub>2</sub>)<sub>m</sub>-O-, wherein m is 1, 2 or 3.

In a more preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula VI, wherein AC represents -(CH<sub>2</sub>)<sub>n</sub>COOH, wherein n is 0, 1 or 2; and R' represents hydrogen; and R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano;  
30 and if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen.

In an even more preferred embodiment the aryl ureido benzoic acid derivative of the invention is a compound of Formula VIIa,



wherein

- 5 AC represents  $-(CH_2)_nCOOH$ , wherein  $n$  is 0, 1 or 2;  
 R' represents hydrogen or alkyl;  
 R<sup>1</sup> represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano;  
 R<sup>2</sup> represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and  
 R<sup>5</sup> and R<sup>6</sup>, independently of each another, represent hydrogen, halo, alkyl,  
 10 cycloalkyl, hydroxy, alkoxy and/or haloalkyl.

In a most preferred embodiment the aryl ureido benzoic acid derivative of the invention is

4-Chloro-2-[3-(9-oxo-9H-fluoren-3-yl)-ureido]-benzoic acid;

- or an enantiomer or a mixture of enantiomers, or a pharmaceutically-  
 15 acceptable addition salt thereof.

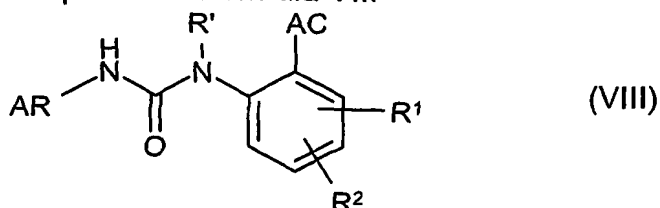
- In a ninth preferred embodiment AR represents an aromatic mono-, bi- or poly-cyclic heterocyclic group, which aromatic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl,  
 20 nitro, cyano, phenyl or benzyl; or which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; and AC, R', R<sup>1</sup> and R<sup>2</sup> are as defined above.

- In a more preferred embodiment AR represents an aromatic 5-membered monocyclic heterocyclic group selected from furanyl, thienyl and pyrrolyl; or an  
 25 aromatic 6-membered monocyclic heterocyclic group selected from pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl; or an aromatic bicyclic heterocyclic group selected from indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thienyl, benzimidazolyl and benzothiazolyl; which aromatic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-  
 30 alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; and AC, R', R<sup>1</sup> and R<sup>2</sup> are as defined above.

In an even more preferred embodiment AC represents  $-SO_2OH$ ;  $-SO_2NH_2$ ; or a group of the formula  $-(CH_2)_nCOOH$ , wherein  $n$  is 0, 1 or 2; and R' represents hydrogen or alkyl; or R' and X together form a heterocyclic ring, which heterocyclic ring

may in particular be a pyrazole, an isoxazole or a pyridazole ring; and  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen.

5 In a further preferred embodiment and the aryl ureido benzoic acid derivative of the invention is a compound of Formula VIII



wherein

AC represents  $-\text{SO}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}_2$ , or  $-\text{COOH}$ ;

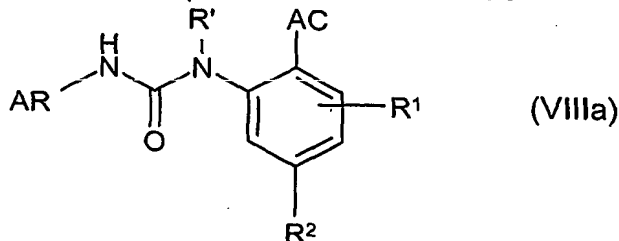
$R'$  represents hydrogen or alkyl;

$R^1$  represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano;

$R^2$  represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

AR represents thienyl, pyridyl or indolyl.

10 In a still further preferred embodiment and the aryl ureido benzoic acid derivative of the invention is a compound of Formula VIIIa



wherein

AC represents  $-\text{SO}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}_2$ , or  $-\text{COOH}$ ;

$R'$  represents hydrogen or alkyl;

$R^1$  represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl;

$R^2$  represents halo, alkyl, cycloalkyl or haloalkyl; and

AR represents 2- or 3-thienyl, 2-, 3- or 4-pyridyl or 2- or 3-indolyl.

In a most preferred embodiment the aryl ureido benzoic acid derivative of the invention is

4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid;

4-Chloro-2-(3-thiophen-2-yl-ureido)-benzoic acid;

4-Chloro-2-(3-pyridin-2-yl-ureido)-benzoic acid;

4-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-5-methyl-benzenesulfonic acid; or

4-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzenesulphonic acid;

or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

#### Definition of Substituents

In the context of this invention halo represents a fluorine, a chlorine, a bromine or an iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms ( $C_{1-18}$ -alkyl), more preferred of from one to six carbon atoms ( $C_{1-6}$ -alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a  $C_{1-4}$ -alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a  $C_{1-3}$ -alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a haloalkyl group designates an alkyl group as defined herein, which alkyl group is substituted one or more times with halo, as defined above. Preferred haloalkyl groups of the invention include trihalomethyl, in particular trifluoromethyl, and trihalomethyl, in particular 2,2,2-trifluoroethyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms ( $C_{2-8}$ -alkenyl), more preferred of from two to six carbon atoms ( $C_{2-6}$ -alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl (allyl); 1-, 2- or 3-butenyl, or 1,3-butadienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-octenyl, or 1,3-octadienyl, or 1,3,5-octatrienyl, or 1,3,5,7-octtetraenyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to eight carbon atoms ( $C_{2-8}$ -alkynyl), more preferred of from two to six carbon atoms ( $C_{2-6}$ -alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butylnyl, or 1,3-butadiynyl; 1-, 2-, 3-, 4-pentylnyl, or 1,3-pentadiynyl; 1-, 2-, 3-, 4-, or 5-henylnyl, or 1,3-hexdiynyl or 1,3,5-hextriynyl; 1-, 2-, 3-, 4-, 5- or 6-heptynyl, or 1,3-heptdiynyl, or 1,3,5-hepttriynyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-octynyl, or 1,3-octdiynyl, or 1,3,5-octtriynyl, or 1,3,5,7-octtetraynyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C<sub>3-7</sub>-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a  
5 cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the  
10 invention include methoxy and ethoxy.

In the context of this invention an aromatic mono-, bi- or poly-cyclic carbocyclic group is a mono-, bi- or poly-cyclic carbocyclic group holding carbon only as ring atom. Preferred aromatic carbocyclic groups of the invention include phenyl, indenyl, naphthyl, azulenyl, fluorenyl, and anthracenyl.

15 In the context of this invention an aromatic mono-, bi- or poly-cyclic heterocyclic group is a mono-, bi- or polycyclic compound, which holds one or more heteroatoms in its ring structure. The term "bi- and poly-heterocyclic groups" includes benzo-fused five- and six-membered heterocyclic rings containing one or more heteroatoms. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur  
20 (S).

Preferred aromatic monocyclic heterocyclic groups of the invention include 5- and 6 membered heterocyclic groups, including furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2 or 3-thienyl; selenophenyl, in particular 2- or 3-selenophenyl; pyrrolyl (azolyl), in particular 2 or 3-pyrrolyl; oxazolyl, in particular  
25 oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 2 or 4-imidazolyl; pyrazolyl, in particular 3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-oxadiazol-4 or 5-yl, or 1,3,4-oxadiazol-2-yl; triazolyl, in particular 1,2,3-triazol-4-yl or 1,2,4-triazol-3-yl; thiadiazolyl, in particular 1,2,3-thiadiazol-4 or 5-yl, or 1,3,4-thiadiazol-2-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,4- or 1,3,5-triazinyl.

Preferred aromatic bicyclic heterocyclic groups of the invention include indoliziny, in particular 2,5 or 6-indoliziny; indolyl, in particular 2,5 or 6-indolyl;  
35 isoindolyl, in particular 2,5 or 6-isoindolyl; benzo[b]furanyl, in particular 2,5 or 6-benzofuranyl; benzo[b]thienyl, in particular 2,5 or 6-benzothieryl; benzoimidazolyl, in particular 2,5 or 6-benzoimidazolyl; benzothiazolyl, in particular 5 or 6-benzothiazolyl; purinyl, in particular 2 or 8-purinyl; quinolinyl, in particular 2,3,6 or 7-quinolinyl; isoquinolinyl, in particular 3,6 or 7-isoquinolinyl; cinnolinyl, in particular 6 or 7-



cinnolinyl; phthalazinyl, in particular 6 or 7-phthalazinyl; quinazolinyl, in particular 2,6 or 7-quinazolinyl; quinoxalinyl, in particular 2 or 6-quinoxalinyl; 1,8-naphthyridinyl, in particular 1,8-naphthyridin-2,3,6 or 7-yl; and pteridinyl, in particular 2,6 or 7-pteridinyl.

#### 5 Pharmaceutically Acceptable Salts

The aryl ureido derivatives of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

10 Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the  
15 enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

20 Metal salts of the aryl ureido derivatives of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

#### Steric Isomers

25 The aryl ureido derivatives of the invention may exist in (+) and (-) forms as well as in racemic forms ( $\pm$ ). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of  
30 an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts  
35 for example.

The aryl ureido derivatives of the invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphoric acid or by

the formation of diastereomeric carbamates by reaction of the chemical compound of the invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in 5 "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

### Methods of Preparation

10 The aryl ureido derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

15 Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

20

### Biological Activity

The aryl ureido derivatives of the present invention were found to be modulators of the ionotropic glutamate receptors, and in particular of the ionotropic GluR5 receptor. In a preferred embodiment the invention the aryl ureido derivatives are 25 useful as selective, non-competitive antagonists of the ionotropic GluR5 receptor.

It is currently believed that compounds that modify neurotransmission by interaction with the aspartate and glutamate receptors are useful in the treatment of a variety of disorders of the CNS and PNS and disorders of other origin, including chronic or acute pain, neuropathic pain, intractable pain, migraine headaches, neurological 30 and psychiatric disorders, depression, anxiety, psychosis, schizophrenia, excitatory amino acid-dependent psychosis, cognitive disorders, dementia, senile dementia, AIDS-induced dementia, stress-related psychiatric disorders, stroke, global and focal ischaemic or haemorrhagic stroke, cerebral hypoxia/ischaemia, cerebral infarction or cerebral ischaemia resulting from thromboembolic or haemorrhagic stroke, cardiac 35 infarction, brain trauma, brain oedema, cranial/brain trauma, spinal cord trauma, bone-marrow lesions, hypoglycaemia, anoxia, neuronal damage following hypoglycaemia, hypotonia, hypoxia, perinatal hypoxia, cardiac arrest, acute and chronic neurodegenerative diseases or disorders and brain ischaemia of various origin, CNS degenerative disorders, Parkinson's disease, Alzheimer's disease, Huntington's

disease, idiopathic and drug induced Parkinson's Disease, amyotrophic lateral sclerosis (ALS), post-acute phase cerebral lesions or chronic diseases of the nervous system, cerebral deficits subsequent to cardiac bypass surgery and grafting, perinatal asphyxia, anoxia from drowning, pulmonary surgery and cerebral trauma, hypoxia-  
5 induced nerve cell damage (e.g. in cardiac arrest or bypass operation, or neonatal distress), epilepsy, status epilepticus, seizure disorders, cerebral vasospasm, CNS-mediated spasms, motility disorders, muscular spasms, urinary incontinence, convulsions, disorders responsive to anticonvulsants, autoimmune diseases, emesis, nausea, obesity, chemical dependencies and addictions, addictions and withdrawal  
10 symptoms, drug or alcohol induced deficits, drug addiction, ocular damage, retinopathy, retinal neuropathy, tinnitus, tardive dyskinesia.

In a more preferred embodiment the aryl ureido derivatives of the invention are used for the treatment of cognitive and neurodegenerative disorders, movement disorders, depression, AD, ADHD, psychosis and associated cognitive deficits, drug-  
15 induced psychosis, drug withdrawal symptoms, stroke, pain, in particular chronic or acute pain, neuropathic pain, intractable pain, or migraine and migraine headaches, epilepsy and retinopathy.

In a particularly preferred embodiment the aryl ureido derivatives of the invention are used for the treatment of pain, in particular chronic or acute pain,  
20 neuropathic pain and intractable pain, migraine, migraine headaches.

In another particularly preferred embodiment the aryl ureido derivatives of the invention are used for the treatment of epilepsy, status epilepticus or a seizure disorder.

## 25 **Pharmaceutical Compositions**

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the aryl ureido derivative the invention.

While the aryl ureido derivative of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the  
30 active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the aryl ureido derivative of the invention, or a  
35 pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

### Methods of Therapy

In another aspect the invention provides a method for the diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of an aspartate or a glutamate receptor, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof.

The preferred indications contemplated according to the invention are those stated above.

In a preferred embodiment, the disorder, disease or condition is chronic or acute pain, neuropathic pain, intractable pain, migraine or migraine headaches.

In a more preferred embodiment, the disorder, disease or condition is epilepsy, status epilepticus or a seizure disorder.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject  
5 involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

## EXAMPLES

10 The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

### Example 1

#### Preparatory Example

15 Starting materials

2-Amino-4-chloro-benzenesulfonic acid

Concentrated sulphuric acid (specific gravity. 1.84) (13.9 ml, 250 mmol) was diluted with 100 ml of water. 3-Chloro-aniline (31.9 g, 250 mmol) was added over 30 minutes while temperature was kept at 85°C. During the addition some precipitation  
20 occurred. The suspension was allowed to cool to room temperature and heavy precipitation was formed. The solid is filtered with suction to yield white crystalline solid. The solid was heated slowly to 200°C under vacuum (water pump) and fitted with a water trap. The solid was kept at 200°C for 7 hours. Water was lost from the crystalline material. The solid was allowed to cool and then dissolved in dilute aqueous  
25 NaOH and precipitated with hydrochloric acid. Yielded 25 g (48%) of the title compound as a white crystalline solid (m.p. > 250°C).

2-Amino-4-chloro-N-hydroxy-benzamide

2-Amino-4-chloro-benzonitrile (5.3 g, 35 mmol) was dissolved in ethanol  
30 (180 ml) aided by heating. An aqueous solution of hydroxylamine hydrochloride (4.9 g, 70 mmol) and sodium bicarbonate (11.1 g, 105 mmol) was added and the mixture was refluxed for 8 hours. The solvent was then reduced and the product suspended in water (100 ml) and filtered off to yield 5.6 g (86%) of a white powder (m.p. 131-133°C).

35 3-(2-Amino-4-chloro-phenyl)-4H-[1,2,4]oxadiazol-5-one

Sodium metal (0.92 g, 40 mmol) was dissolved in 70 ml absolute ethanol and 2-amino-4-chloro-N-hydroxy-benzamide (3.71 g, 20 mmol) was added and then diethyl carbonate (9.44 g, 80 mmol) was added. The mixture was refluxed for 18 hours and then reduced to dryness under vacuum and triturated with 0.5 M aqueous HCl,

filtered and then triturated with toluene and filtered to yield 3.4 g (80%) of red-brown solid (m.p. 159-161°C).

### Individual Methods

5 2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-5-methyl-benzenesulfonic acid (Compound 1a)

2-Amino-4-chloro-5-methyl-benzenesulfonic acid (665 mg, 3.0 mmol) was suspended in 30 ml dry THF and 1-bromo-3-isocyanato-benzene (624 mg, 3.15 mmol) was added. Upon addition of triethylamine (354 mg, 3.15 mmol) the suspension cleared and became a solution. The solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (150 ml) and washed with diluted aqueous hydrochloric acid. The organic phase was dried over sodium sulphate and reduced to dryness under vacuum. The title compound was recrystallised from ethyl acetate / heptane to give 820 mg (65%) of white crystals (m.p. 275°C; decomposition).

15 6-Chloro-3-hydroxy-indazole-1-carboxylic acid naphthalen-2-ylamide (Compound 1b)

2-Amino-4-chloro-benzoic acid (17.16 g, 100 mmol) was suspended in 90 ml of water and 20 ml of concentrated HCl. NaNO<sub>2</sub> (6.9 g, 100 mmol) was dissolved in 15 ml water and added slowly at 0°C. The mixture was stirred at 0°C for 30 minutes and Na<sub>2</sub>SO<sub>3</sub> (34.0 g, 270 mmol) were added, dissolved in 150 ml water. The mixture was then stirred for 2 hours at room temperature. 30 ml of concentrated HCl were added and the mixture stirred overnight at room temperature and then at 80°C for 2 hours. The solution is treated with aqueous NaOH until the pH is 5.5 and the precipitated was filtered and triturated with ethanol to yield 13.8 g (82%) of 6-chloro-1H-indazol-3-ol. 6-Chloro-1H-indazol-3-ol (700 mg, 4.15 mmol) was dissolved in 25 ml pyridine together with 1-bromo-3-isocyanato-benzene (990 mg, 5 mmol) and stirred at RT for 4 hours. The mixture was then diluted with EtOAc (100 ml) and washed 2x with 1 M HCl. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub> and reduced under vacuum. The residue was now dissolved in 1 M NaOH and washed with EtOAc and then precipitated with HCl and the precipitate extracted into EtOAc, dried and reduced under vacuum. The product was then recrystallised from EtOAc and heptane to yield 1.1 g (79%) of crystalline solid (m.p. 223-225°C).

35 {2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-phenyl}-acetic acid (Compound 1c)

6-Chlorooxindole (2.5 g, 14.9 mmol) was suspended in 50 ml 4 M aqueous NaOH and the mixture was refluxed for 6 hours. The reaction mixture was allowed to cool and the product precipitated and filtered off with suction. The solid was dissolved in water (100 ml) and precipitated with 4 M aqueous HCl at 0°C. The solid was then filtered with suction and dried under vacuum to yield 2.0 g (72%) of white crystalline

solid. (2-Amino-4-chloro-phenyl)-acetic acid (700 mg, 3.8 mmol) was then dissolved in 25 ml pyridine and 1-bromo-3-isocyanato-benzene (811 mg, 4.1 mmol) was added drop-wise and the solution was stirred for 90 minutes. The reaction mixture was diluted with 150 ml ethyl acetate and washed twice with 1 M aqueous HCl. The organic phase  
5 was reduced under vacuum and the product recrystallised from ethyl acetate / heptane to yield 680 mg of white crystalline solid (47%) (m.p. 195-196°C)

### Method A

#### 2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-benzenesulfonic acid, triethylammonium salt

##### 10 (Compound A1)

2-Amino-4-chloro-5-benzenesulfonic acid (623 mg, 3 mmol) was suspended in 40 ml dry THF and 1-bromo-3-isocyanato-benzene (693 mg, 3.5 mmol) was added. Upon addition of triethylamine (354 mg, 3.5 mmol) the suspension cleared and became a solution. The solution was stirred at room temperature for 1 hour. The  
15 reaction mixture was reduced to dryness under vacuum. The title compound was recrystallised from ethyl acetate / heptane to give 1060 mg (70%) of white crystals (m.p. 178-179°C) of the title compound.

#### 4-Chloro-5-methyl-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic acid,

##### 20 triethylammonium salt

##### (Compound A2)

Was made according to method A (m.p. 182-183°C).

#### 4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic acid, triethyl-

##### 25 ammonium salt

##### (Compound A3)

Was made according to method A (m.p. 174-176°C).

### Method B

##### 30 4-Chloro-2-[3-(1H-indol-2-yl)-ureido]-5-methyl-benzenesulfonic acid (Compound B1)

Indole-2-carboxylic acid (1.29 g, 8.0 mmol) was suspended in 20 ml dry toluene and diphenyl-phosphoryl azide (2.64 g, 9.6 mmol) added. Triethylamine (0.816 g, 8.0 mmol) was then added drop-wise and the mixture stirred at room temperature for 0.5 hour. The solution was heated to 80°C and the suspension cleared  
35 immediately. Then 2-Amino-4-chloro-5-methyl-benzenesulfonic acid (1.661 g, 8.0 mmol) was added and triethylamine (0.816 g, 8.0 mmol). The mixture was stirred for 3 hours at 80°C and then the reaction mixture was diluted with 200 ml ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was then extracted 3 times with distilled water. The title compound was precipitated from the  
40 aqueous phase with addition of HCl, filtered and recrystallised from ethyl acetate /

heptane to yield 1.6 g (53%) of title compound as light purple crystalline solid (m.p. 284-286°C; decomposition).

4-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzensulphonic acid (Compound B2)

5 Was made according to method B (m.p. 277-279°C; decomposition).

**Method C**

4-Chloro-2-(3-phenyl-ureido)-benzoic acid (Compound C1)

2-Amino-4-chloro-benzoic acid (515 mg, 3.0 mmol) was suspended in dry  
10 THF (5 ml) and phenylisocyanate (429 mg, 3.6 mmol) was added. Triethylamine (303 mg, 3.0 mmol) was added and the mixture was stirred for 2 hours. The mixture was diluted with 75 ml ethyl acetate and extracted into 150 ml 1 M aqueous NaOH, and washed once with 50 ml ethyl acetate. The aqueous phase was then acidified with 4 M aqueous HCl and the product extracted with 2 x 100 ml ethyl acetate. The organic  
15 solvent was dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced under vacuum, and the product recrystallised from acetone/water to yield 680 mg (78%) of off-white crystals (m.p. 186-188°C).

4-Chloro-2-[3-(2-methoxy-phenyl)-ureido]-benzoic acid (Compound C2)

20 Was made using method C (m.p. 181-183°C).

2-(3-Benzo[1,3]dioxol-5-yl-ureido)-4-chloro-benzoic acid (Compound C3)

Was prepared using method C (m.p. 183-185°C)

4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzoic acid (Compound C4)

25 Was prepared using method C (m.p. 179-182°C)

2-(3-Biphenyl-2-yl-ureido)-4-chloro-benzoic acid (Compound C5)

Was prepared using method C (m.p. 208-209°C).

30 2-(3-Biphenyl-4-yl-ureido)-4-chloro-benzoic acid (Compound C6)

Was prepared using method C (m.p. 193-194°C).

2-[3-(2-Bromo-phenyl)-ureido]-4-chloro-benzoic acid (Compound C7)

35 Was prepared using method C (m.p. 195-197°C).

4-Chloro-2-[3-(4-fluoro-phenyl)-ureido]-benzoic acid (Compound C8)

Was prepared using method C (m.p. 194-195°C).

4-Chloro-2-[3-(4-iodo-phenyl)-ureido]-benzoic acid (Compound C9)

40 Was prepared using method C (m.p. 209-210; decomposition).



4-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzoic acid (Compound C10)

Was prepared using method C (m.p. 205-207°C).

4-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid (Compound C11)

5 Was prepared using method C (m.p. 192-193°C).

4-Chloro-2-[3-(4-methoxy-phenyl)-ureido]-benzoic acid (Compound C12)

Was prepared using method C (m.p. 194-195°C).

10 4-Chloro-2-[3-(2-trifluoromethyl-phenyl)-ureido]-benzoic acid (Compound C13)

Was prepared using method C (m.p. 173-175°C).

4-Chloro-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid (Compound C14)

Was prepared using method C (m.p. 207-209°C).

15

**Method D**1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea(Compound D1)

20 3-(2-Amino-4-chloro-phenyl)-4H-[1,2,4]oxadiazol-5-one (400 mg, 1.92 mmol) was dissolved in 20 ml dry THF and 3-trifluoromethyl-phenyl-isocyanate (450 mg, 2.40 mmol) was added and the reaction stirred for 16 hours. The solvent was reduced under vacuum and the product recrystallised from ethyl acetate and heptane to yield 480 mg (63%) of off-white crystalline solid (m.p. 246-248; decomposition).

25

1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-bromo-phenyl)-urea (Compound D2)

Was made using method D (m.p. 210-211°C; decomposes).

30 **Method E**

4-Chloro-2-(3-pyridin-2-yl-ureido)-benzoic acid (Compound E1)

Pyridine-2-carboxylic acid (369 mg, 3 mmol) was suspended in 15 ml dry toluene and diphenyl-phosphoryl azide (958 mg, 3.5 mmol) added. Triethylamine (354 mg, 3.6 mmol) was then added drop-wise and the mixture stirred at room temperature for 0.5 hour. The solution was heated to 80°C and after 2 hours 2-amino-4-chloro-benzoic acid (463 mg, 2.7 mmol) was added in 20 ml THF and triethylamine (0.354 g, 3.6 mmol) was also added. The mixture was stirred for 1 hour at 80°C and then at room temperature overnight. The mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was taken up into ethyl acetate and

precipitated with heptane and filtered with suction. Yield after recrystallation from ethyl acetate / heptane was 640 mg (73%) of white crystalline solid (m.p. 222-224°C).

4-Chloro-2-(3-naphtalen-2-yl-ureido)-benzoic acid (Compound E2)

5 Was made using method E (m.p. 176-179°C).

4-Chloro-2-[3-(9-oxo-9H-fluoren-3-yl)-ureido]-benzoic acid (Compound E3)

Was made using method E (m.p. 260-263°C; decomposition).

10 4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid (Compound E4)

Was made using method E (m.p. 198-201°C).

4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid (Compound E5)

Was made using method E (M.p. >300°C).

15

4-Chloro-5-methyl-2-(3-naphthalen-2-yl-ureido)-benzensulphonic acid (Compound E6)

Was prepared using method E (m.p. >300°C).

1-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-3-naphthalen-2-yl-urea (Compound E7)

20

Was prepared using method E (m.p. 167-169°C; decomposition).

1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-naphthalen-2-yl-urea (Compound E8)

Was prepared using method E (m.p. 245°C; decomposition).

25

2-(3-Biphenyl-3-yl-ureido)-4-chloro-benzoic acid (Compound E9)

*p*-Iodo-benzoic acid (4.96 g, 20 mmol), phenyl boronic acid (2.68 g, 22 mmol), Na<sub>2</sub>CO<sub>3</sub> (6.36 g, 60 mmol) and Pd(OAc)<sub>2</sub> (44 mg) were dissolved in 80 ml water and heated to 50°C for 1 hour. Filtered and washed EtOAc, then acidified with 1 M HCl and extracted into EtOAc, dried with Na<sub>2</sub>SO<sub>4</sub>, evaporated and recrystallised from EtOAc and heptane to yield 3.9 g of meta-phenyl benzoic acid as a white solid. 2-(3-Biphenyl-3-yl-ureido)-4-chloro-benzoic acid was then prepared according to method E (m.p. 181-183°C).

30

35 4-Chloro-2-(3-thiophen-2-yl-ureido)-benzoic acid (Compound E10)

Was prepared using method E (m.p. 199-200°C)

**Method F**

4-Chloro-2-[3-(4-hydroxy-phenyl)-ureido]-benzoic acid (Compound F1)

40

4-Chloro-2-[3-(2-methoxy-phenyl)-ureido]-benzoic acid (430 mg, 1.5 mmol) was suspended in 100 ml CH<sub>2</sub>Cl<sub>2</sub> at 0°C, and BBr<sub>3</sub> (1.8 ml, 1.0 M in hexane, 1.8 mmol)

was added. The mixture was stirred overnight and more  $\text{BBr}_3$  (0.9 ml, 1.0 M in hexane, 0.9 mmol) was added followed by additional stirring overnight. The mixture was wash with water and reduced under vacuum. The title compounds was recrystallised from acetone/water to yield 310 mg (73%) white solid (m.p. 212-214°C; decomposition).

5

4-Chloro-2-[3-(3-hydroxy-phenyl)-ureido]-benzoic acid (Compound F2)

Was prepared using method F (m.p. 209-211°C).

4-Chloro-2-[3-(2-hydroxy-phenyl)-ureido]-benzoic acid (Compound F3)

10

Was prepared using method F (m.p. 179-180°C; decomposition).

## Example 2

### GluR5 and GluR6 Functional Assay

This example describes cell-based assays carried out using human  
15 embryonic HEK 293 cells stably expressing GluR5 and GluR6 receptors, respectively, in which assays the inhibition of domoate-induced increase in  $\text{Ca}_i$  is used as a measure for glutamate antagonist activity of test substances.

The intracellular free calcium concentration ( $\text{Ca}_i$ ) is regulating the majority of metabolic processes in mammalian cells. Elevations of  $\text{Ca}_i$  in excitable tissues such as  
20 neurones are seen after specific activation of receptor operated calcium channels (e.g. glutamate receptors), or after depolarisation and opening of voltage operated calcium channels. Some neurotransmitters and neuro-modulator increase  $\text{Ca}_i$  by activating G-protein coupled ionophors or by release of  $\text{Ca}_i$  from intracellular stores via the second messenger  $\text{IP}_3$ .

$\text{Ca}_i$  is determined by fluorometric methods in a Fluorescent Image Plate  
25 Reader (FLIPR). Calcium-chelating fluorochromes (tetracarboxylic acids) are loaded into the cells as acetoxymethyl esters and subsequently released by an unspecific intracellular esterase. The free acids, which are impermeable to the cell membrane, are maintained in the cell for hours. The fluorescence spectrum (either  $\text{EX}_{\text{max}}$ ,  $\text{EM}_{\text{max}}$   
30 or both) is changed by the binding of calcium, and the fluorescence is directly proportional to the  $\text{Ca}_i$ .

The present method uses the fluorochromes Fluo-3 or Fluo-4 as the calcium-chelator. Fluo-3/Fluo-4 is virtually non-fluorescent without calcium, but the calcium-Fluo-3/Fluo-4 complexes show a bright fluorescence ( $\text{EM}_{\text{max}} = 526 \text{ nm}$ ) after  
35 excitation around 500 nm ( $\text{EX}_{\text{max}} = 505 \text{ nm}$ ). This fluorescence spectrum is similar to the spectrum of fluorescein. Since excitation and emission is in the visible light region of the spectrum, standard equipment without quartz optics may be used.

The kainate subtype of ionotropic glutamate receptors exists of two high affinity subunits - KA1 and KA2, and three low affinity subunits - GluR5-7. The ion

channel in the GluR5 receptor subtype can be made permeable for calcium by substitution of an arginine (R) to a glutamine (Q) in the pore region. The stably expressed human GluR5 receptors used here are calcium permeable (Q), which makes them ideal for fluorescence measurements.

5

#### Cell culture

GluR5 expressing, respectively GluR6 expressing HEK 293 cells are grown in DMEM containing 10% foetal calf serum, in polystyrene culture flasks (175 cm<sup>2</sup>) in a humidified atmosphere of 5% CO<sub>2</sub> in air, at 37°C. Confluence of cells should be 80-100% on day of plating. GluR5 cells are rinsed with 10 ml of PBS, then added 1.5 ml of Trypsin-EDTA and left in the incubator for 5 min. After addition of 10 ml of growth media cells are re-suspended by trituration with a 10 ml pipette 15 times.

The cells are seeded at a density of 0.5-1x10<sup>6</sup> cells/ml (100 µl/well) in black-walled, clear bottom, 96-well plates pre-treated with 0.001% PEI solution (75 µl/well for ≥30 min). Plated cells were allowed to proliferate for 24 h before loading with dye.

#### Loading with Fluo-4-AM

Fluo-4-AM (1 mg, Molecular Probes) is added 912 µl DMSO containing 25 mg/150 µl Pluoronic F-127 (Molecular Probes). The Fluo-4-AM stock solution (1 mM) is diluted with DMEM to a final concentration of 2 µM Fluo-4-AM.

The media is removed from the wells, and 50 µl of the Fluo-4-AM loading solution is added to each well. The plate is sealed and incubated at room temperature for 60 min.

#### Calcium measurements

After the loading period, the loading media is aspirated and the cells are washed twice with 100 µl Na<sup>+</sup> free Ringer (NN: 10 mM HEPES, 140 mM Choline chloride, 5 mM KCl, 1 mM MgCl<sub>2</sub>, 10 mM CaCl<sub>2</sub>, pH 7.4) to remove extracellular dye. 100 µl NN is added to each well, and the fluorescence is measured in the FLIPR.

Cells are pre-incubated for 1.5 min with test compound (50 µl) before addition of domoate (50 µl) to a final concentration of 2 µM when determined on GluR5 and 0.2 µM when determined on GluR6.

Stock solutions of test substances are made in 48% ethanol, 50% DMSO or 100% DMSO. The final concentration of ethanol or DMSO in the well must not exceed 0.1%. Dilutions are done in NN in clear V-bottom plates.

#### FLIPR settings

Temperature: 25°C

Preincubation: 50 µl test solution at a rate of 30 µl/sec and starting height of 100 µl

40

Antagonist phase: 50  $\mu$ l domoate solution (8  $\mu$ M) at a rate of 35  $\mu$ l/sec and starting height of 150  $\mu$ l

Reading intervals: preincubation - 10 sec x 7 and 3 sec x 3  
antagonist phase - 3 sec x 17 and 10 sec x 12

5

Addition plates (diluted compound plate and domoate plate) are placed on the far right and left positions in the FLIPR tray. Cell plates are placed in the middle position. Run the preincubation phase test first by using the above settings. The FLIPR will pick up the desired amount from the compound plate and pipette into the cell plate.

10 FLIPR will then take the appropriate measurements in accordance with the interval settings above.

### Results

Fluorescence at stimulation with domoate or test substance is corrected for  
15 the mean basal fluorescence (in NN).

Fluorescence of domoate in the presence of test substance is expressed relative to the domoate response alone.

25-75% inhibition of the domoate stimulation must be obtained before calculating the IC<sub>50</sub>.

20 The test value will be given as IC<sub>50</sub> (the concentration ( $\mu$ M) of test substance, which inhibits 50% of the domoate induced Ca<sub>i</sub> elevation), calculated either from a concentration/response curve or from the formula

$$IC_{50} = (\text{applied test substance concentration, } \mu\text{M}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

25

where C<sub>o</sub> is domoate stimulated Ca<sub>i</sub> accumulation in control assays, and C<sub>x</sub> is the domoate stimulated Ca<sub>i</sub> in the presence of test compound.

The result of this determination is presented in Table 1 below.

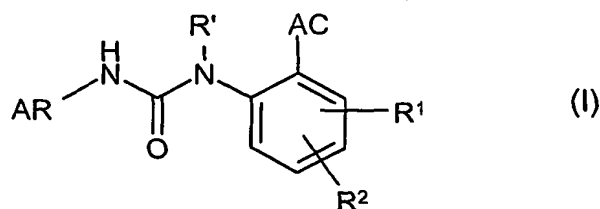
### 30 Table 1

#### Functional Data

Compound No.	GluR5 Activity	GluR6 Activity
35	IC <sub>50</sub> ( $\mu$ M)	
Compound 1a	1.1	32
Compound A1	1.5	10
Compound E2	1.2	70
40 Compound C14	1.3	37

## CLAIMS

1. A aryl ureido derivative represented by Formula I,



any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

AC represents an acidic group selected from

-SO<sub>2</sub>OH;

-SO<sub>2</sub>NH<sub>2</sub>;

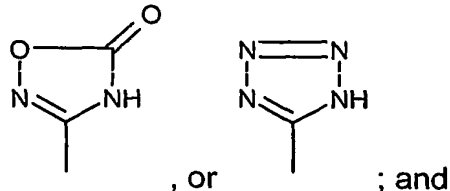
a group of the formula -(CH<sub>2</sub>)<sub>n</sub>COOH, wherein n is 0, 1, 2 or 3;

a group of the formula -(CX)OH, wherein

X represents O or NR'', wherein R'' represents hydrogen or alkyl; or

X together with R' form a heterocyclic ring; and

a heterocyclic ring of the structure



R' represents hydrogen or alkyl; or

R' and X together form a heterocyclic ring; and

R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, haloalkyl, nitro or cyano; and

if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen; and

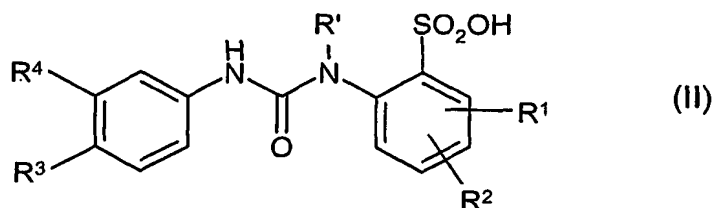
AR represents an aromatic mono-, bi- or polycyclic carbocyclic or heterocyclic group,

which aromatic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure -O-(CH<sub>2</sub>)<sub>m</sub>-O-, wherein m is 1, 2 or 3.

2. The aryl ureido derivative of claim 1, wherein  
 AR represents an aromatic mono-, bi- or poly-cyclic carbocyclic group,  
 which aromatic carbocyclic group is optionally substituted one or more times with  
 substituents selected from the group consisting of halo, alkyl, cycloalkyl,  
 cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano,  
 phenyl or benzyl; or  
 which aromatic group is optionally substituted with a methylenedioxy group or a  
 higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3.

3. The aryl ureido derivative of claim 2, represented by Formula II,



wherein

R' represents hydrogen or alkyl; or

R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, haloalkyl, nitro or cyano; and

if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen; and

R<sup>3</sup> and R<sup>4</sup>, independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

R<sup>3</sup> and R<sup>4</sup> together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3; or

R<sup>3</sup> and R<sup>4</sup> together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

4. The aryl ureido derivative of claim 3, wherein

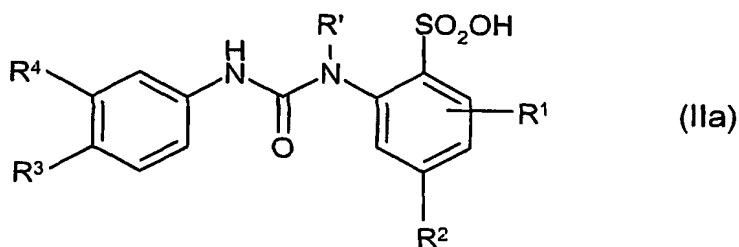
R' represents hydrogen or alkyl; and

$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl or cycloalkyl; and  
if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano or phenyl; or

$R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  
 $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

5. The aryl ureido derivative of claim 4, represented by Formula IIa,



wherein,

$R'$  represents hydrogen or alkyl; and

$R^1$  represents hydrogen, halo, alkyl or cycloalkyl; and

$R^2$  represents halo, alkyl or cycloalkyl; and

$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl; or

$R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or  
 $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

6. The aryl ureido derivative of claim 5, which is

2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-5-methyl-benzenesulfonic acid;

4-Chloro-5-methyl-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic acid;

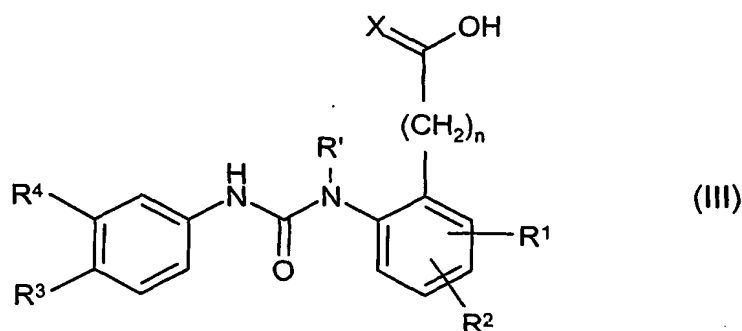
4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzenesulphonic acid;

2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-benzenesulfonic acid; or



4-Chloro-5-methyl-2-(3-naphthalen-2-yl-ureido)-benzenesulphonic acid;  
or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable  
addition salt thereof.

- 5 7. The aryl ureido derivative of claim 2, represented by Formula III,



wherein

- 10 n is 0, 1 or 2;

X represents O or NR'', wherein R'' represents hydrogen or alkyl; or  
R' and X together form a heterocyclic ring; and

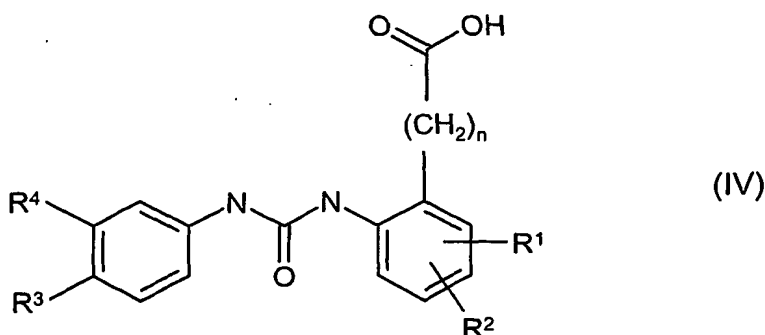
- 15 R' represents hydrogen or alkyl; or  
R' and X together form a heterocyclic ring; and

- R<sup>1</sup> and R<sup>2</sup>, independently of each other, represents hydrogen, halo, alkyl,  
cycloalkyl, haloalkyl, nitro or cyano; and  
20 if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different  
from hydrogen; and

- R<sup>3</sup> and R<sup>4</sup>, independently of each other, represent hydrogen, halo, alkyl,  
cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro,  
25 cyano, phenyl or benzyl; or

- R<sup>3</sup> and R<sup>4</sup> together form a methylenedioxy ring or a higher homolog of the  
structure -O-(CH<sub>2</sub>)<sub>m</sub>-O-, wherein m is 1, 2 or 3; or  
R<sup>3</sup> and R<sup>4</sup> together form a benzo-fused ring, which fused ring is optionally  
substituted one or more times with substituents selected from halo, alkyl,  
30 cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro,  
cyano, phenyl or benzyl.

8. The aryl ureido derivative of claim 7, represented by Formula IV,



wherein

5      n is 0, 1 or 2; and

$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

10      if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

15       $R^3$  and  $R^4$  together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3; or

20       $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

9. The aryl ureido benzoic acid derivative of claim 8, wherein

25      n is 0, 1 or 2; and

$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl or cycloalkyl; and

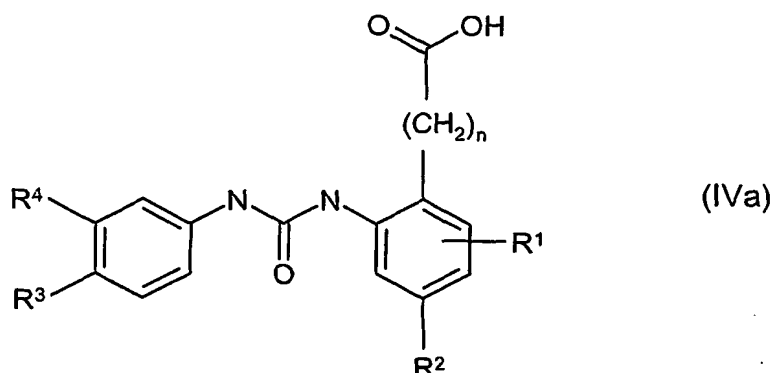
if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

30       $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl, nitro, cyano or phenyl; or

$R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or

$R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

- 5 10. The aryl ureido benzoic acid derivative of claim 9, represented by Formula IVa,



wherein

- 10 n is 0 or 1; and

$R^1$  represents hydrogen, halo, alkyl or cycloalkyl; and  
 $R^2$  represents halo, alkyl or cycloalkyl; and

- 15  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl or phenyl; or

$R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or

- 20  $R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

11. The aryl ureido derivative of claim 10, which is

4-Chloro-2-(3-phenyl-ureido)-benzoic acid;

4-Chloro-2-[3-(2-methoxy-phenyl)-ureido]-benzoic acid;

- 25 2-(3-Benzo[1,3]dioxol-5-yl-ureido)-4-chloro-benzoic acid;

4-Chloro-2-[3-(3-trifluoromethyl-phenyl)-ureido]-benzoic acid;

2-(3-Biphenyl-2-yl-ureido)-4-chloro-benzoic acid;

2-(3-Biphenyl-4-yl-ureido)-4-chloro-benzoic acid;

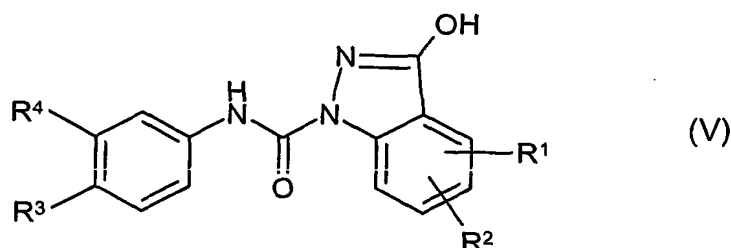
2-[3-(2-Bromo-phenyl)-ureido]-4-chloro-benzoic acid;

- 30 4-Chloro-2-[3-(4-fluoro-phenyl)-ureido]-benzoic acid;

4-Chloro-2-[3-(4-iodo-phenyl)-ureido]-benzoic acid;

4-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzoic acid;

- 4-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(4-methoxy-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(2-trifluoromethyl-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;  
 5 4-Chloro-2-(3-naphtalen-2-yl-ureido)-benzoic acid;  
 4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid;  
 2-(3-Biphenyl-3-yl-ureido)-4-chloro-benzoic acid;  
 4-Chloro-2-[3-(4-hydroxy-phenyl)-ureido]-benzoic acid;  
 4-Chloro-2-[3-(3-hydroxy-phenyl)-ureido]-benzoic acid;  
 10 4-Chloro-2-[3-(2-hydroxy-phenyl)-ureido]-benzoic acid; or  
 {2-[3-(3-Bromo-phenyl)-ureido]-4-chloro-phenyl}-acetic acid;  
 or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable  
 addition salt thereof.
- 15 12. The aryl ureido benzoic acid derivative of claim 7, which is a phenyl carbamoyl  
 indazole derivative of Formula V,



wherein

20  $R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

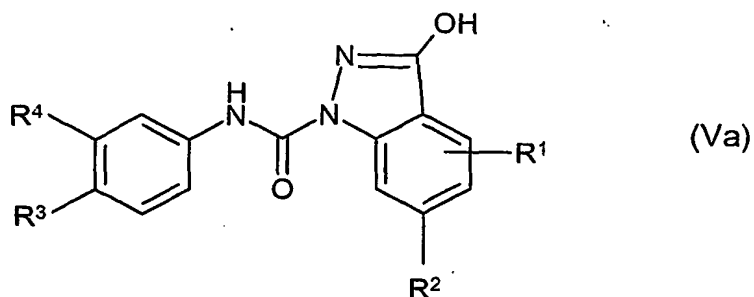
if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

25  $R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

30  $R^3$  and  $R^4$  together form a methylenedioxy ring or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein  $m$  is 1, 2 or 3; or

$R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl.

13. The aryl ureido benzoic acid derivative of claim 12, represented by Formula Va,



wherein

R<sup>1</sup> represents hydrogen, halo, alkyl or cycloalkyl;

R<sup>2</sup> represents halo, alkyl or cycloalkyl; and

R<sup>3</sup> and R<sup>4</sup>, independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl, nitro, cyano or phenyl; or

R<sup>3</sup> and R<sup>4</sup> together form a methylenedioxy ring or a higher homolog of the structure -O-CH<sub>2</sub>-O-; or

R<sup>3</sup> and R<sup>4</sup> together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

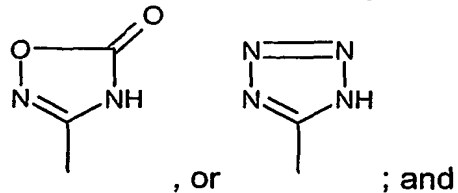
14. The aryl ureido benzoic acid derivative of claim 13, which is

6-Chloro-3-hydroxy-indazole-1-carboxylic acid naphthalen-2-ylamide;

or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

15. The aryl ureido benzoic acid derivative of claim 1, wherein

AC represents a heterocyclic ring of the structure



R' represents hydrogen or alkyl; and

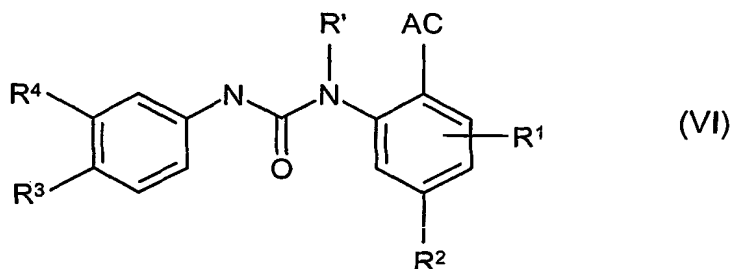
$R^1$  and  $R^2$ , independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and  
if one of  $R^1$  and  $R^2$  represents hydrogen, then the other of  $R^1$  and  $R^2$  is different from hydrogen; and

AR represents an aromatic mono-, bi- or polycyclic carbocyclic or heterocyclic group,

which aromatic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

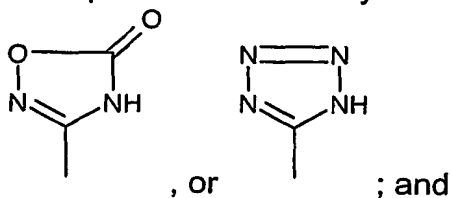
which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3.

16. The aryl ureido benzoic acid derivative of claim 15, represented by Formula VI,



wherein

AC represents a heterocyclic ring of the structure



$R'$  represents hydrogen or alkyl;

$R^1$  represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano;

$R^2$  represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

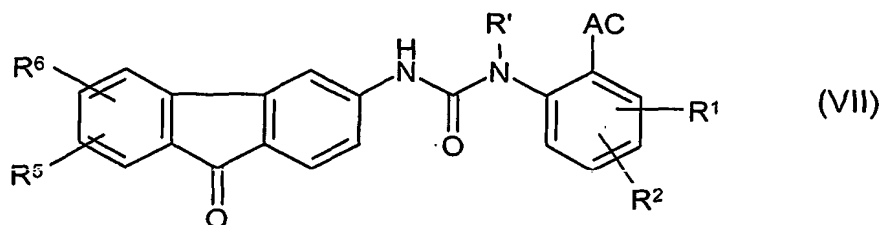
$R^3$  and  $R^4$ , independently of each another, represent hydrogen, halo, hydroxy, alkoxy, haloalkyl or phenyl; or

$R^3$  and  $R^4$  together form a methylenedioxy ring of the structure  $-O-CH_2-O-$ ; or

$R^3$  and  $R^4$  together form a benzo-fused ring, which fused ring is optionally substituted one or more times with substituents selected from halo, hydroxy, alkoxy and haloalkyl.

- 5 17. The aryl ureido benzoic acid derivative of claim 16, which is  
 1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea;  
 1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-(3-bromo-phenyl)-urea;  
 10 1-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-3-naphthalen-2-yl-urea; or  
 1-[5-Chloro-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-3-naphthalen-2-yl-urea;  
 or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

- 15 18. The aryl ureido benzoic acid derivative of claim 1, represented by Formula VII,



wherein

AC represents an acidic group selected from

-SO<sub>2</sub>OH;

-SO<sub>2</sub>NH<sub>2</sub>;

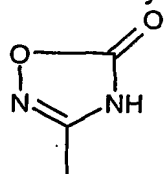
a group of the formula -(CH<sub>2</sub>)<sub>n</sub>COOH, wherein n is 0, 1, 2 or 3;

a group of the formula -(CX)OH, wherein

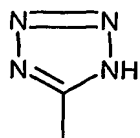
X represents O or NR'', wherein R'' represents hydrogen or alkyl; or

X together with R' form a heterocyclic ring; and

a heterocyclic ring of the structure



, and



; and

R' represents hydrogen or alkyl; or

R' and X together form a heterocyclic ring; and

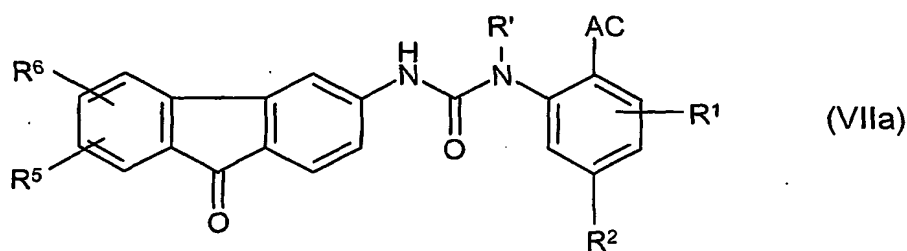
R<sup>1</sup> and R<sup>2</sup>, independently of each other, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen; and

R<sup>5</sup> and R<sup>6</sup>, independently of each other, represent hydrogen, halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or

R<sup>5</sup> and R<sup>6</sup> together form a methylenedioxy ring or a higher homolog of the structure -O-(CH<sub>2</sub>)<sub>m</sub>-O-, wherein m is 1, 2 or 3.

19. The aryl ureido benzoic acid derivative of claim 18, represented by Formula VIIa,



AC represents -(CH<sub>2</sub>)<sub>n</sub>COOH, wherein n is 0, 1 or 2; and

R' represents hydrogen or alkyl; and

R<sup>1</sup> represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

R<sup>2</sup> represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

R<sup>5</sup> and R<sup>6</sup>, independently of each other, represent hydrogen, halo, alkyl, cycloalkyl, hydroxy, alkoxy and/or haloalkyl.

20. The aryl ureido benzoic acid derivative of claim 19, which is

4-Chloro-2-[3-(9-oxo-9H-fluorene-3-yl)-ureido]-benzoic acid;

or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

21. The aryl ureido derivative of claim 1, wherein



AR represents an aromatic mono-, bi- or poly-cyclic heterocyclic group, which aromatic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; or  
which aromatic group is optionally substituted with a methylenedioxy group or a higher homolog of the structure  $-O-(CH_2)_m-O-$ , wherein m is 1, 2 or 3; and

AC, R', R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1.

22. The aryl ureido derivative of claim 21, wherein

AR represents

an aromatic 5-membered monocyclic heterocyclic group selected from furanyl, thienyl and pyrrolyl; or  
an aromatic 6-membered monocyclic heterocyclic group selected from pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl; or  
an aromatic bicyclic heterocyclic group selected from indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thienyl, benzimidazolyl and benzothiazolyl;  
which aromatic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, hydroxy, alkoxy, oxo, haloalkyl, nitro, cyano, phenyl or benzyl; and

AC, R', R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1.

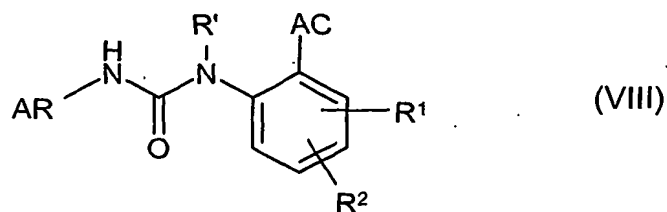
23. The aryl ureido derivative of claim 22, wherein

AC represents  $-SO_2OH$ ;  $-SO_2NH_2$ ; or a group of the formula  $-(CH_2)_nCOOH$ , wherein n is 0, 1 or 2; and

R' represents hydrogen or alkyl; and

R<sup>1</sup> and R<sup>2</sup>, independently of each another, represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and  
if one of R<sup>1</sup> and R<sup>2</sup> represents hydrogen, then the other of R<sup>1</sup> and R<sup>2</sup> is different from hydrogen.

24. The aryl ureido benzoic acid derivative of claim 23, represented by Formula VIII,



AC represents -SO<sub>2</sub>OH, -SO<sub>2</sub>NH<sub>2</sub>, or -COOH; and

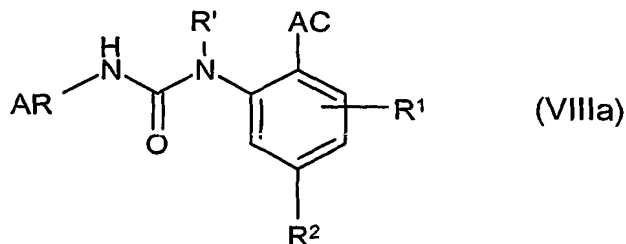
R' represents hydrogen or alkyl; and

R<sup>1</sup> represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

R<sup>2</sup> represents halo, alkyl, cycloalkyl, haloalkyl, nitro or cyano; and

AR represents thienyl, pyridyl or indolyl.

25. The aryl ureido benzoic acid derivative of claim 23, represented by Formula VIIIa,



AC represents -SO<sub>2</sub>OH, -SO<sub>2</sub>NH<sub>2</sub>, or -COOH; and

R' represents hydrogen or alkyl; and

R<sup>1</sup> represents hydrogen, halo, alkyl, cycloalkyl, haloalkyl; and

R<sup>2</sup> represents halo, alkyl, cycloalkyl or haloalkyl; and

AR represents 2- or 3-thienyl, 2-, 3- or 4-pyridyl or 2- or 3-indolyl.

26. The aryl ureido benzoic acid derivative of claim 25, which is

4-Chloro-2-[3-(2-iodo-phenyl)-ureido]-benzoic acid;

4-Chloro-2-(3-thiophen-2-yl-ureido)-benzoic acid;

4-Chloro-2-(3-pyridin-2-yl-ureido)-benzoic acid;

4-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-5-methyl-benzenesulfonic acid; or

4-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzensulphonic acid;  
or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof.

- 5 27. A pharmaceutical composition comprising a therapeutically effective amount of a chemical compound of claims 1-26, or a pharmaceutically-acceptable addition salt thereof.
- 10 28. Use of a chemical compound of claims 1-26, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/-medicament.
- 15 29. Use of a chemical compound of claims 1-26, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the ionotropic GluR5 receptor.
- 20 30. The use according to claim 29, wherein the disease, disorder or condition is chronic or acute pain, neuropathic pain, intractable pain, migraine headaches, neurological and psychiatric disorders, depression, anxiety, psychosis, schizophrenia, excitatory amino acid-dependent psychosis, cognitive disorders, dementia, senile dementia, AIDS-induced dementia, stress-related psychiatric disorders, stroke, global and focal ischaemic or haemorrhagic stroke, cerebral hypoxia/ischaemia, cerebral infarction or cerebral ischaemia resulting from thromboembolic or haemorrhagic stroke, cardiac infarction, brain trauma, brain oedema, cranial/brain trauma, spinal cord trauma, bone-marrow lesions, hypoglycaemia, anoxia, neuronal damage following hypoglycaemia, hypotonia, hypoxia, perinatal hypoxia, cardiac arrest, acute and chronic neurodegenerative diseases or disorders and brain ischaemia of various origin, CNS degenerative disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease, idiopathic and drug induced Parkinson's Disease, amyotrophic lateral sclerosis (ALS), post-acute phase cerebral lesions or chronic diseases of the nervous system, cerebral deficits subsequent to cardiac bypass surgery and grafting, perinatal asphyxia, anoxia from drowning, pulmonary surgery and cerebral trauma, hypoxia-induced nerve cell damage (e.g. in cardiac arrest or bypass operation, or neonatal distress), epilepsy, status epilepticus, seizure disorders, cerebral vasospasm, CNS-mediated spasms, motility disorders, muscular spasms, urinary incontinence, convulsions, disorders responsive to
- 35

anticonvulsants, autoimmune diseases, emesis, nausea, obesity, chemical dependencies and addictions, addictions and withdrawal symptoms, drug or alcohol induced deficits, drug addiction, ocular damage, retinopathy, retinal neuropathy, tinnitus, tardive dyskinesia.

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31. The use according to claim 29, wherein the disorder, disease or condition is chronic or acute pain, neuropathic pain, intractable pain, migraine or migraine headaches.

10 32. The use according to claim 29, wherein the disorder, disease or condition is epilepsy, status epilepticus or a seizure disorder.

15 33. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of an aspartate or a glutamate receptor, which method comprises the step of administering to said animal body in need thereof a therapeutically effective amount of a chemical compound as described in claims 1-26, or a pharmaceutically-acceptable addition salt thereof.

20

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**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,  
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
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MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,  
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,  
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent  
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ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,  
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EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for all designations

**Published:**

- with international search report

(88) Date of publication of the international search report:  
19 August 2004

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: ARYL UREIDO DERIVATIVES AND THEIR MEDICAL USE

(57) Abstract: This invention relates to novel aryl ureido benzoic acid derivatives useful as selective and non-competitive antagonists of the ionotropic GluR5 receptor. Due to their biological activity, the aryl ureido derivatives of the invention are considered useful for treating diseases that are responsive to modulation of an aspartate or a glutamate receptor. Moreover the invention provides chemical compounds for use according to the invention, as well as pharmaceutical compositions comprising the chemical compounds, and methods of treating diseases or disorders or conditions responsive to modulation of an aspartate or a glutamate receptor.

WO 2004/046090 A3

## INTERNATIONAL SEARCH REPORT

 Inte Application No  
 PCT/DK 03/00768

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 C07C275/42 C07C309/46 C07D209/40 C07D213/72 C07D231/56  
 C07D257/04 C07D271/07 C07D333/36 A61K31/17 A61K31/19  
 A61K31/381 A61K31/416 A61K31/4245 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 24707 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 4 May 2000 (2000-05-04) claims; examples	1-30
X	WO 98 47879 A (NEUROSEARCH AS ;PEDERSEN OVE (DK); CHRISTOPHERSEN PALLE (DK)) 29 October 1998 (1998-10-29) claims; examples	1-30
X	WO 99 38846 A (PATCH RAYMOND ;PROCEPT INC (US); FENG BAINIAN (US); OCAIN TIMOTHY) 5 August 1999 (1999-08-05) page 31 -page 33	1-30
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## ° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

19 April 2004

Date of mailing of the international search report

04.06.2004

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# INTERNATIONAL SEARCH REPORT

Inte Application No  
PCT/DK 03/00768

## G(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 00357 A (VERTEX PHARMA) 7 January 1999 (1999-01-07) compound 125, page 33 and page 4, line 17 - line 32	1-30
X	--- US 6 417 393 B1 (PEDERSEN OVE ET AL) 9 July 2002 (2002-07-09) claims; examples	1-30
X	--- WO 02 39987 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 23 May 2002 (2002-05-23) claims	1,2, 7-10,27, 28
X	--- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BENNEKOU, POUL ET AL: "Treatment with NS3623, a novel Cl-conductance blocker, ameliorates erythrocyte dehydration in transgenic SAD mice: a possible new therapeutic approach for sickle cell disease" retrieved from STN Database accession no. 2001:169674 CAPLUS XP002277267 abstract & BLOOD, vol. 97, no. 5, 2001, pages 1451-1457, ISSN: 0006-4971	1,2,15, 16,27,28
X	--- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BUCKMAN, BRAD O. ET AL: "Solution-phase parallel synthesis of benzoxazines using a polymer-supported carbodiimide" retrieved from STN Database accession no. 1998:159564 CAPLUS XP002277268 abstract & TETRAHEDRON LETTERS, vol. 39, no. 12, 1998, pages 1487-1488, ISSN: 0040-4039	1,2,7-10
X	--- US 2 722 544 A (HENRY MARTIN) 1 November 1955 (1955-11-01) examples	1-5
X	--- GB 709 455 A (VARIAPAT AG) 26 May 1954 (1954-05-26) examples	1-5
	--- -/--	

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/DK 03/00768

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 656 350 A (SQUIBB BRISTOL MYERS CO) 7 June 1995 (1995-06-07) the whole document	1-33
A	WO 94 22807 A (NEUROSEARCH AS ;OLESEN SOEREN PETER (DK); MOLDT PETER (DK); PEDERS) 13 October 1994 (1994-10-13) the whole document	1-33
A	WO 97 29743 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE LOUISA (US); VEBER DA) 21 August 1997 (1997-08-21) the whole document	1-33
A	WO 96 25157 A (HERTZBERG ROBERT PHILIP ;JUREWICZ ANTHONY JOSEPH (US); RUTLEDGE ME) 22 August 1996 (1996-08-22) the whole document	1-33
A	MICHAEL R. PAVIA ET AL: "N-Phenyl-N'-pyridinylureas as anticonvulsant agents1" J. MED. CHEM., vol. 33, 1990, pages 854-861, XP002277266 ISSN: 0022-2623 the whole document	1-33



# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/DK 03/00768

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-5, 6-10, 21-25, 27-28  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 33

Claim 33 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Claims Nos.: 1-5, 6-10, 21-25, 27-28

The aryl ureido derivative represented by Formula I in claim 1 is so generally formulated that the search revealed a very large number of compounds relevant for the issue of novelty. A selection of relevant documents have been cited.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK/00768

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0024707	A	04-05-2000	AU 759275 B2	10-04-2003
			AU 6325999 A	15-05-2000
			BR 9914638 A	03-07-2001
			CA 2342626 A1	04-05-2000
			CN 1322194 T	14-11-2001
			WO 0024707 A1	04-05-2000
			EE 200100185 A	15-08-2002
			EP 1123274 A1	16-08-2001
			HU 0103673 A2	28-02-2002
			JP 2002528432 T	03-09-2002
			JP 2003246773 A	02-09-2003
			NO 20011956 A	20-04-2001
			NZ 510098 A	26-09-2003
			PL 347371 A1	08-04-2002
			SK 5222001 A3	09-05-2002
			TR 200101126 T2	21-09-2001
			US 2002032210 A1	14-03-2002
			US 2002037905 A1	28-03-2002
			ZA 200101824 A	05-03-2002
WO 9847879	A	29-10-1998	AT 226189 T	15-11-2002
			AT 248824 T	15-09-2003
			AU 735545 B2	12-07-2001
			AU 2962197 A	05-01-1998
			AU 728520 B2	11-01-2001
			AU 6919698 A	13-11-1998
			BR 9808938 A	01-08-2000
			CA 2255858 A1	04-12-1997
			CA 2285424 A1	29-10-1998
			CN 1118462 B	20-08-2003
			DE 69716424 D1	21-11-2002
			DE 69716424 T2	20-02-2003
			DE 69817802 D1	09-10-2003
			DE 69817802 T2	08-04-2004
			WO 9847879 A1	29-10-1998
			DK 977741 T3	01-12-2003
			WO 9745400 A1	04-12-1997
			EP 0906273 A1	07-04-1999
			EP 0977741 A1	09-02-2000
			JP 2000511167 T	29-08-2000
			JP 2001521532 T	06-11-2001
			NZ 332789 A	26-05-2000
			NZ 337976 A	25-05-2001
			RU 2197482 C2	27-01-2003
			SI 977741 T1	31-12-2003
			SK 144799 A3	16-05-2000
			TR 9902593 T2	21-03-2000
			US 6417393 B1	09-07-2002
			US 6297261 B1	02-10-2001
			US 2002037905 A1	28-03-2002
WO 9938846	A	05-08-1999	AU 2108099 A	16-08-1999
			WO 9938846 A1	05-08-1999
WO 9900357	A	07-01-1999	US 6093742 A	25-07-2000
			AU 8377698 A	19-01-1999
			CA 2294463 A1	07-01-1999
			EP 0993441 A1	19-04-2000

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No

PCT/DK 03/00768

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900357	A	WO 9900357 A1	07-01-1999
US 6417393	B1	09-07-2002	
		AT 226189 T	15-11-2002
		AU 735545 B2	12-07-2001
		AU 2962197 A	05-01-1998
		AU 2962297 A	05-01-1998
		CA 2255858 A1	04-12-1997
		DE 69716424 D1	21-11-2002
		DE 69716424 T2	20-02-2003
		WO 9745400 A1	04-12-1997
		WO 9745111 A1	04-12-1997
		EP 0906273 A1	07-04-1999
		EP 0910358 A1	28-04-1999
		JP 2000511167 T	29-08-2000
		JP 2000510862 T	22-08-2000
		NZ 332789 A	26-05-2000
		AT 248824 T	15-09-2003
		AU 728520 B2	11-01-2001
		AU 6919698 A	13-11-1998
		BR 9808938 A	01-08-2000
		CA 2285424 A1	29-10-1998
		CN 1118462 B	20-08-2003
		DE 69817802 D1	09-10-2003
		DE 69817802 T2	08-04-2004
		WO 9847879 A1	29-10-1998
		DK 977741 T3	01-12-2003
		EP 0977741 A1	09-02-2000
		JP 2001521532 T	06-11-2001
		NZ 337976 A	25-05-2001
		RU 2197482 C2	27-01-2003
		SI 977741 T1	31-12-2003
		SK 144799 A3	16-05-2000
		TR 9902593 T2	21-03-2000
		US 6297261 B1	02-10-2001
		US 2002037905 A1	28-03-2002
WO 0239987	A	23-05-2002	
		AU 2349202 A	27-05-2002
		WO 0239987 A2	23-05-2002
US 2722544	A	01-11-1955	NONE
GB 709455	A	26-05-1954	NONE
EP 0656350	A	07-06-1995	
		US 5547966 A	20-08-1996
		AU 690133 B2	23-04-1998
		AU 7446394 A	27-04-1995
		CA 2132771 A1	08-04-1995
		EP 0656350 A1	07-06-1995
		JP 7188151 A	25-07-1995
WO 9422807	A	13-10-1994	
		AT 175955 T	15-02-1999
		AU 683654 B2	20-11-1997
		AU 6537894 A	24-10-1994
		CA 2160128 A1	13-10-1994
		DE 69416119 D1	04-03-1999
		DE 69416119 T2	27-05-1999
		WO 9422807 A1	13-10-1994
		EP 0693053 A1	24-01-1996

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No  
PCT/DK 03/00768

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422807	A	CA 2160128 A1	13-10-1994
		DE 69416119 D1	04-03-1999
		DE 69416119 T2	27-05-1999
		WO 9422807 A1	13-10-1994
		EP 0693053 A1	24-01-1996
		FI 954746 A	17-11-1995
		JP 8510448 T	05-11-1996
		KR 266846 B1	15-09-2000
		NO 953956 A	07-12-1995
		NZ 265052 A	19-12-1997
		US 5696138 A	09-12-1997
WO 9729743	A	21-08-1997	
		AU 725456 B2	12-10-2000
		AU 6900796 A	02-09-1997
		BG 102690 A	30-04-1999
		BR 9612779 A	24-10-2000
		CA 2245927 A1	21-08-1997
		CA 2432662 A1	21-08-1997
		CN 1215990 A	05-05-1999
		CZ 9802569 A3	17-02-1999
		EA 1436 B1	26-02-2001
		EP 0809492 A1	03-12-1997
		EP 0896531 A1	17-02-1999
		HU 0000467 A2	28-05-2000
		JP 11503110 T	23-03-1999
		JP 2000504722 T	18-04-2000
		NO 983737 A	14-10-1998
		NZ 316710 A	26-05-2000
		PL 328562 A1	01-02-1999
		SK 110198 A3	11-02-1999
		TR 9801592 T2	21-05-1999
		WO 9729743 A1	21-08-1997
		US 6180675 B1	30-01-2001
		US 6005008 A	21-12-1999
WO 9625157	A	22-08-1996	
		EP 0809492 A1	03-12-1997
		JP 11503110 T	23-03-1999
		NO 983737 A	14-10-1998
		WO 9625157 A1	22-08-1996
		US 6180675 B1	30-01-2001
		US 5886044 A	23-03-1999
		US 5780483 A	14-07-1998